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Health Effects Assessment for Cadmium

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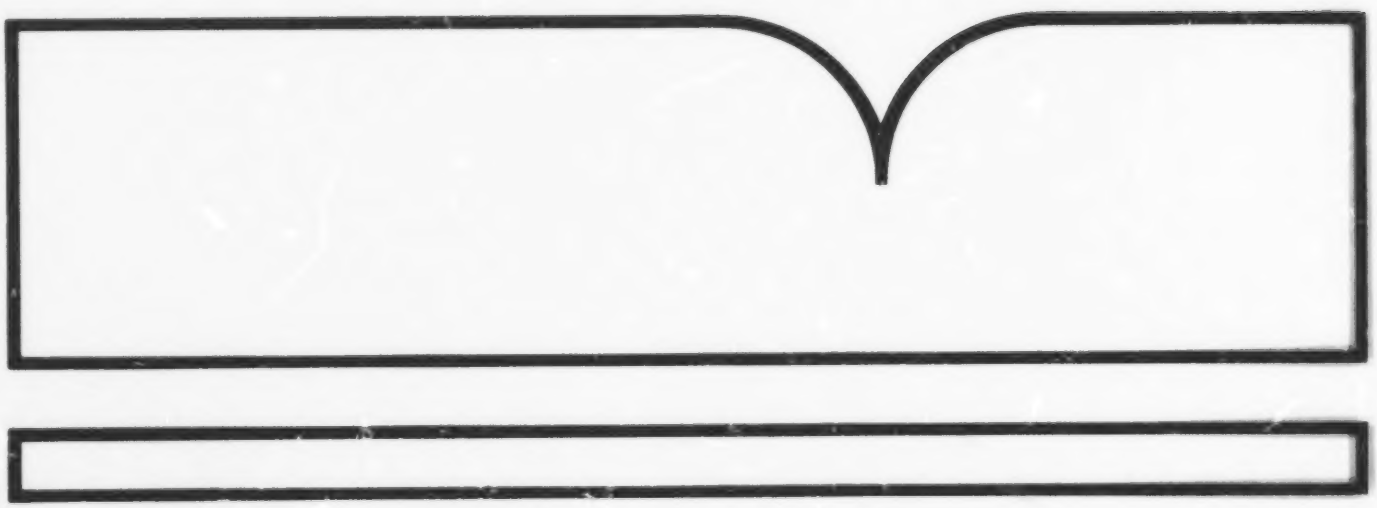

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HEALTH EFFECTS ASSESSMENT FOR CADMIUM

U.S. Environmental Protection Agency
Office of Research and Development
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Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
Washington, DC 20460

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16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

A chronic interim acceptable intake was determined for cadmium based on oral exposure. A q_1^* was determined for cadmium based on inhalation exposure.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with cadmium. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Cadmium. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-025. NTIS PB 81-117368.

U.S. EPA. 1982. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of Cadmium and Compounds. Prepared by Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983a. Reportable Quantity for Cadmium (and compounds). Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Updated mutagenicity and carcinogenicity assessment of cadmium. Carcinogen Assessment Group, OHEA. EPA 600/8-83-025B. NTIS PB 85-116150.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is

assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983b).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of quantitative estimates presented.

A dose-related increase in lung carcinoma has been reported in rats exposed to cadmium chloride aerosols. Cadmium exposure has been linked to excess respiratory cancers in cadmium smelter workers. The CAG (U.S. EPA, 1984) has estimated an upper bound unit risk for continuous inhalation exposure of 2.228×10^{-3} $\mu g/m^3$ cadmium based on human data for respiratory cancers. From this data a unit risk of 7.8 $(mg/kg/day)^{-1}$ was calculated. The CAG document was in draft form at the time of this review.

Evidence is currently inadequate to consider cadmium a carcinogen through the oral route. As a result of the ubiquitous nature of the compound and chronic baseline exposure neither an AIS nor an AIC are suggested. It is proposed that the additional exposure increment through drinking water should not exceed the drinking water standard of 10 $\mu g/\ell$. This value may require revision when the cadmium RMCL is finalized.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
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Editorial review for the document series was provided by:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by:

Bette Zwayer, Pat Daunt, Karen Mann and Jacky Bohanon
Environmental Criteria and Assessment Office
Cincinnati, OH

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CS	Composite score
DNA	Deoxyribonucleic acid
LOEL	Lowest-observed-effect level
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Cadmium is a metal belonging to Group IIB of the Periodic Table. Elemental cadmium has a CAS Registry number of 7440-43-9. It occurs in nature in the zero valence (metal and alloys) and in the +2 valence (compound) states. Besides forming ionic and covalent compounds with anions and groups, cadmium also complexes with ammonia, cyanide, halides and thiocyanate (Hollander and Carapella, 1978).

In the atmosphere cadmium is expected to be present as dust and fumes from smelting of ores, manufacturing of metallic alloys, reprocessing of cadmium-containing alloys, recycling of steel scrap, coal-fired power plants and incineration of solid wastes (Fishbein, 1981). The atmospheric fate of cadmium has not been studied comprehensively. Any chemical interaction of cadmium compounds in the atmosphere is likey to result in speciation (i.e., conversion into a more stable species such as CdO), and not in its direct removal through decomposition, as frequently occurs with organic compounds. The principal removal mechanisms for atmospheric cadmium may occur through wet and dry deposition (Fishbein, 1981). The atmospheric half-life for the physical removal mechanism is expected to depend on the particle size and particle density of atmospheric cadmium. There is considerable evidence that cadmium is concentrated in smaller (<3 μm) particles in the atmosphere (Fishbein, 1981). Therefore, it may have a long half-life in the atmosphere, although no estimate for this half-life is available.

The dominant fate of cadmium in the aquatic media is sedimentation through sorption onto clays or organic matter, coprecipitation and isomorphous substitution in carbonate minerals. Smaller amounts of cadmium may persist in the aquatic phase in solution, either as hydrated cations or as organic or inorganic complexes.

In most unpolluted water, the majority of soluble cadmium may exist as the hydrated cation, whereas in polluted waters, complexation with organic material may be most important (Callahan et al., 1979).

The fate of cadmium in soil has not been studied adequately. However, by analogy with its fate in aquatic media, cadmium is expected to be strongly sorbed in soil, and sorption will increase as the organic matter content of soil increases (Callahan et al., 1979). Conditions that may weaken the sorption process, such as a decrease of pH (<7) and an increase in salinity, may enhance desorption of cadmium from soil. Cadmium is mobile in soil, as evidenced by the detection of this element in 100% of the groundwater samples collected from New Jersey (Page, 1981).

The BCFs for cadmium in aquatic organisms have been determined by several investigators. In freshwater and marine fish the BCF have been found to vary between 1000 and 3000 (Callahan et al., 1979.)

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

Several studies indicate that cadmium is poorly absorbed following oral administration. Friberg et al. (1974) reported that ~2% of orally administered cadmium was absorbed by experimental animals (species and compound not specified in the review). Absorption appears to be slightly more extensive in humans, with reported absorption values of 6 and 4.6% (Rahola et al., 1973; McLellan et al., 1978).

The absorption of orally administered cadmium may be altered by a variety of dietary parameters (Bremner, 1974). Washko and Cousins (1976) found that diets low in calcium result in a significant increase in cadmium absorption. Diets deficient in vitamin D, protein, zinc, iron and copper also increase the extent of cadmium absorption (Worker and Migicovsky, 1961; Suzuki et al., 1969; Banis et al., 1969; Bunn and Matrone, 1966; Hill et al., 1963). Ascorbic acid deficiency has been observed to increase cadmium toxicity (Fox and Fry, 1970).

2.2. INHALATION

Absorption of cadmium from the respiratory tract appears to be much more extensive than absorption from the gastrointestinal tract. Up to 25% of inhaled cadmium dust and aerosols may be absorbed when a large proportion of the particles are in the respirable range and the compound is relatively soluble (U.S. EPA, 1980b). Up to 50% of the cadmium in cadmium fumes or cigarette smoke may be absorbed (WHO Task Group, 1977; Elinder et al., 1976).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

The major effects of long-term exposure to cadmium are similar following both oral and inhalation exposure. Renal dysfunction, resulting in disturbances in mineral metabolism and, eventually, formation of kidney stones or osteomalacia, is the major effect in humans. Pulmonary dysfunction is observed following higher inhalation exposures. Cadmium exposure has been correlated with hypertension in humans.

3.1. SUBCHRONIC

3.1.1. Oral. The subchronic oral toxicity of cadmium is summarized in Table 3-1.

No data were located on the subchronic oral exposure of humans to cadmium. Three subchronic oral toxicity studies and one 3-generation reproduction study investigated the toxic response of rats and mice to cadmium. Schroeder and Mitchener (1971) investigated the effect of 10 mg cadmium (unspecified soluble salt)/ℓ drinking water on reproductive performance in mice. The treated mice failed to reproduce past the second generation. Nearly a third of the offspring died before weaning, and 13.3% of the survivors were classified as runts. Assuming that mice drink 17% of their body weight per day as water, the dose was 1.7 mg Cd/kg bw/day. Fitzhugh and Meiller (1941) observed anemia in rats exposed to similar doses of cadmium (2.25 mg/kg bw/day).

Yuhas et al. (1979) administered cadmium acetate (0, 1, 10 or 100 mg/ℓ) in the drinking water to male Sprague-Dawley rats for 13 weeks. The doses reported in the paper are not consistent with the reported water concentration, water consumption and body weights. Based on the data reported, the correct doses appear to be 0, 0.118, 0.947 and 8.041 mg/kg bw/day. At

TABLE 3-1

Subchronic Oral Toxicity of Cadmium

Compound	Species/Strain/ Sex	Dose	Length of Exposure	Effects	Reference
Cadmium acetate	rat/Sprague-Dawley/M	0, 1, 10 or 100 µg/Cd/ℓ drinking water (118, 947 or 8041 mg/kg bw/day)	13 weeks	Decreased weight gain at 100 µg/ℓ; no effect on cellular structure of liver, kidney or duodenum at any dose; decreased serum alkaline phosphatase in all dose groups; increased cadmium content in bone at 10 and 100 µg/Cd/mℓ H_2O; decreased zinc content of bone at 100 µg/mℓ.	Yuhas et al., 1979
Cadmium chloride	mice/Swiss Webster/NR	3 or 300 µg Cd/ℓ H_2O (0.51 or 51 mg/kg bw/day)	70 days	Decrease in the number of lymphocytes secreting antibodies to sheep red blood cells at both dose levels; necrosis of renal epithelial cells in the proximal convoluted tubules and collecting tubules at both doses	Koller et al., 1975
Cadmium	rats/NR/NR	0, 15, 45, 75 or 135 mg/kg diet (0, 0.75, 2.25, 3.75 or 6.75 mg/kg bw/day)	6 months	Marked anemia, decreased weight gain and increased mortality at 135 mg/kg diet; anemia at doses of 45 and 75 mg/kg diet	Fitzhugh and Meiller, 1941
Unspecified soluble salt	mice/NR/M,F	10 mg/ℓ H_2O (1.7 mg/kg bw/day)	3 generations	Decreased reproductive performance (no 3rd generation); increased postnatal mortality; increased congenital malformations	Schroeder and Mitchener, 1971

NR = Not reported

the high-dose level, weight gain was depressed, the cadmium content of bone was increased, the zinc content of bone was decreased and serum phosphorus concentrations were elevated. At a dose of 0.947 mg/kg bw/day, bone cadmium content was increased. Serum alkaline phosphatase activity was decreased in all dose groups. No histological effects were observed in any dose group.

Koller et al. (1975) administered drinking water containing 3 or 300 mg Cd/ℓ to Swiss Webster mice (390 mice/group) for 70 days. The controls consisted of 80 mice that received deionized water. Mice were immunized with sheep red blood cells during treatment or 1, 7, 14 or 42 days after the end of treatment. The number of lymphocytes secreting antibodies to sheep red blood cells was markedly decreased in both dose groups. There was a dose-related incidence of necrosis of the renal epithelial cells in the proximal convoluted tubules and collecting tubules. Assuming that mice drink water equivalent to 17% of their body weight each day, this corresponds to a dose of 0.51 mg/kg bw/day.

3.1.2. Inhalation. Pertinent data regarding the subchronic inhalation toxicity of cadmium were not located in the available literature.

3.2. CHRONIC

3.2.1. Oral. The chronic oral toxicity of cadmium is summarized in Table 3-2.

Schroeder et al. (1963, 1964, 1965) administered cadmium acetate in the drinking water (5 mg/Cd/ℓ) to Long-Evans rats and Charles River mice for their lifetimes. Survival was decreased in both sexes of rats and in male mice. In rats, treatment was associated with renal and cardiac arteriosclerosis, cardiac hypertrophy and neurological effects. The major effect reported in mice was an altered renal morphology. Renal degeneration and necrosis have also been reported in Wistar rats receiving 123 mg Cd (as cadmium chloride)/ℓdrinking water (Kajikawa et al., 1981).

TABLE 3-2

Chronic Oral Toxicity of Cadmium

Compound	Species/Strain/ Sex	Dose	Length of Exposure	Effects	Reference
Cadmium acetate	rats/Long-Evans/M,F	0 or 5 mg Cd/ℓ H_2O (0 or 0.39 mg Cd/kg bw/day)	lifetime (~2.5 years)	Decreased survival; systolic hypertension; renal and cardiac arteriosclerosis and cardiac hypertrophy; severe vestibular disturbances	Schroeder et al., 1963, 1964, 1965; Kanisawa and Schroeder, 1969
Cadmium acetate	mice/Charles River/M,F	0 or 5 mg Cd/ℓ H_2O (0 or 0.85 mg Cd/kg bw/day	lifetime (~2 years)	Decreased survival in males; hyalinized glomeruli, thickened basement membranes, and a reduction in the lumen/wall ratio in the arterioles of the kidneys	Schroeder et al., 1964; Kanisawa and Schroeder, 1969
Cadmium	rats/Wistar/ NR	0 or 123 mg Cd/ℓ H_2O (0 or 9.57 mg Cd/kg bw/day)	4-91 weeks	Vacuolar degeneration of the kidneys; cellular necrosis in the proximal convoluted tubules; increased urinary protein excretion	Kajikawa et al., 1981
NR	human/NA/ M,F	228 µg/day (estimated LOEL; 30 µg/day for a 70 kg man)	lifetime	Itai-itai disease; tubular proteinuria	Friberg et al., 1974; Muramatsu, 1974; Nogawa et al., 1978; U.S. EPA, 1980b
NR	human/NA/ M,F	250-350 µg Cd/day (estimated LOEL)	50 years	Renal dysfunction	Friberg et al., 1974

NA = Not applicable

NR = Not reported

The U.S. EPA (1980b) has estimated the threshold dose for induction of proteinuria, based upon dietary intake data from areas of Japan in which itai-itai disease is prevalent. In these areas, ~85% of the daily cadmium intake is derived from rice (Muramatsu, 1974). Nogawa et al. (1978) found that the prevalence of tubular proteinuria in persons under 70 did not exceed the prevalence in control populations until the cadmium levels in rice were >0.40-0.49 μg/g rice. The U.S. EPA (1980b) estimated a LOEL of 228 μg Cd/day, using an average value of 0.45 μg Cd/g rice. For a corresponding Western European or American population, the daily dose that would result in an equivalent mg/kg bw/day was estimated to be 301 μg Cd/day.

This LOEL is in good agreement with the estimate of 250-350 μg Cd/day determined by Friberg et al. (1974), based on the "generally accepted" critical cadmium level at which renal dysfunction occurs, 200 μg Cd/g wet weight of renal cortex.

3.2.2. Inhalation. The chronic inhalation toxicity of cadmium is summarized in Table 3-3.

Friberg (1948 a,b, 1950), in a study of workers exposed to cadmium iron oxide dust in a Swedish alkaline battery factory, was the first to observe a correlation between cadmium exposure and the development of emphysema. These findings have since been confirmed by a number of investigators (Paterson, 1947; Baader, 1952; Lane and Campbell, 1954; Buxton, 1956; Smith et al., 1960, 1976; Kazantzis et al., 1963; Potts, 1965; Holden, 1965; Lewis et al., 1969; Snider et al., 1973; Lauwerys et al., 1974). Cadmium-induced emphysema is only observed following inhalation exposure.

TABLE 3-3

Chronic Inhalation Toxicity of Cadmium

Compound	Species/Strain/ Sex	Dose	Length of Exposure	Effects	Reference
Cadmium dust (<5, diameter)	human/NA/M	21 µg Cd/m³ (66 µg total Cd/m³)	21-40 years	Decreased pulmonary ventilatory function; increased incidence of kidney dysfunction; increased proteinuria	Lauwerys et al., 1974
Cadmium fumes	human/NA/NR	125 µg Cd/m³	9 months to 12 years	Anemia; elevated urinary protein levels	Tsuchiya, 1967
Cadmium iron oxide dust	human/NA/NR	NR	NR	Emphysema; proteinuria	Friberg, 1948a,b, 1950

NA = Not applicable

NR = Not reported

Tsuchiya (1967) studied 13 workers who had been exposed to cadmium fumes (TWA = 125 μg Cd/m³) for 9 months to 12 years. The control group consisted of 13 age-matched nonexposed workers. The only effects noted were decreased blood hemoglobin levels and elevated urinary protein levels.

Lauwerys et al. (1974) studied 22 male workers who were exposed to an average respirable cadmium dust (<5 μ, aerodynamic diameter) concentration of 21 μg Cd/m³ for 21-40 years. The total airborne cadmium concentration averaged 66 μg Cd/m³. The control group was matched to the exposed group by age, sex, weight, height, smoking habits and socioeconomic status. Kidney dysfunction, as indicated by proteinuria, was observed in 68% of the cadmium-exposed group as compared with 15% in the control group. Measures of pulmonary ventilatory function (forced vital capacity, forced expiratory volume/second, and peak expiratory flow rate) were reduced in the cadmium-exposed group.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Dixon et al. (1976) reported that a concentration of 0.1 mg cadmium/ℓ administered to rats in their drinking water for 90 days produced no detectable effects on reproduction. At a higher concentration (10 mg cadmium/ℓ), Schroeder and Mitchener (1971) reported the induction of decreased fertility, runting, young deaths and sharp angulation of the distal third of the tail in a three-generation reproduction study in rodents. Cadmium has also been demonstrated to be teratogenic and to reduce fertility following intravenous, intraperitoneal and subcutaneous administration (U.S. EPA, 1980b).

3.3.2. Inhalation. No data pertinent to the teratogenicity or other reproductive effects of inhaled cadmium were located in the available literature.

3.4. TOXICANT INTERACTIONS

The absorption and toxicity of cadmium may be altered by a number of dietary factors. These are discussed in Section 2.1. In experimental animals, zinc has been reported to prevent or reduce cadmium-induced testicular damage, teratogenic effects, growth inhibition and tumor induction (Parizek, 1957; Parizek et al., 1969; Ferm and Carpenter, 1967; Gunn et al., 1963a,b, 1964). Increased dietary copper has been demonstrated to prevent or reduce mortality, anemia and degeneration of aortic elastin (Hill et al., 1963; Bunn and Matrone, 1966). Dietary cadmium inhibits intestinal absorption of copper and calcium, possibly leading to deficiencies of these elements (Starcher, 1969; Ando et al., 1977; Kobayashi, 1970).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the oral carcinogenicity of cadmium in humans were not located in the available literature.

4.1.2. Inhalation. It is beyond the scope and resources of the present document to present all of the available epidemiologic data concerning cadmium and cancer. The Carcinogen Assessment Group (CAG) has prepared an excellent in-depth review of the evidence available concerning the carcinogenicity of cadmium (U.S. EPA, 1984). The reader is referred to this document for a summary and critical review of the literature. The conclusions drawn from their review were that the weight of the evidence suggests a significant risk of lung cancer from exposure to cadmium; however, the evidence that cadmium is a potent lung carcinogen is not compelling.

The considered opinion presented in this document is that the data presented by Thun et al. (1984) provide the strongest evidence for cadmium as a causative agent in human cancer. Briefly, this study examines a cohort of cadmium smelter workers who were employed for at least 2 years in a production capacity within one plant between January 1, 1940 and December 31, 1969. This cohort had a total of 16 deaths from respiratory cancer through December 31, 1978; 6.99 deaths from this cause would have been expected based on calendar time age-specific death rates for white males in the United States.

The CAG points out several problems associated with using this study for risk assessment purposes:

1. Smoking rate may have been higher for this cohort as compared to the general population.
2. Exposure is confounded by exposure to arsenic, a known respiratory carcinogen.

3. Very limited characterization of exposure levels and duration.

4. No exposure estimates for individuals.

5. Available data do not allow evaluation of goodness of fit for the mathematical model(s) used in risk assessment.

Despite these reservations, the CAG feels that a risk assessment based on these data could be useful. The cancer response did correspond in terms of site to animal response. In addition, the confounding factors should increase the apparent cancer risk thus producing an upper-bound estimate.

4.2. BIOASSAYS

4.2.1. Oral. Schroeder et al. (1964) administered drinking water containing cadmium acetate (5 μg Cd/mℓ H_2O) to a group of 48 male and 39 female mice for the lifetime of the animals. Significant decreases in the incidence of pulmonary tumors and total tumor incidence were observed in the cadmium-treated animals; however, mean survival time was also reduced.

Levy et al. (1975) administered weekly doses of cadmium sulfate by gavage to groups of 50 male Swiss mice (0.44, 0.88 or 1.75 mg Cd/kg bw) for 18 months. No tumors of the prostate gland were detected.

Schroeder et al. (1965) and Kanisawa and Schroeder (1969) administered cadmium acetate (5 μg Cd/mℓ drinking water) to Long-Evans rats for the lifetime of the animals. No significant differences were observed in total tumor incidence or the incidence of any specific tumor type between treated and control groups.

Levy and Clark (1975) administered weekly doses of 0.09, 0.18 or 0.35 mg Cd/kg bw as cadmium sulfate to groups of 30 male CB hooded rats by gavage for 2 years. There was no treatment-related increase in either the total tumor incidence or the incidence of prostate tumors.

Decker et al. (1958) administered cadmium chloride (0.1, 0.5, 2.5, 5.0 or 10.0 mg Cd/ℓ drinking water) to groups of eight male and eight female Sprague-Dawley rats for 1 year. No tumors were found that could be attributed to cadmium treatment. Loser (1980) and Sato (1977) also failed to find an association between oral administration of cadmium and the development of tumors.

4.2.2. Inhalation. Paterson (1947) reported a study in which rats were exposed to cadmium oxide and cadmium chloride fumes; however, IARC (1976) concluded that the duration of exposure was too short to draw any conclusions from the reported absence of tumors.

Takenaka et al. (1983) exposed male Wistar rats to three concentrations of cadmium chloride aerosols. Measured cadmium chloride concentrations averaged 50.8, 25.7 and 13.4 $\mu g/m^3$ for the three groups, respectively. Forty rats were included in each cadmium group plus 41 rats exposed to filtered air. Animals were exposed continuously for 18 months. Following the treatment period animals were kept an additional 13 months and then sacrificed.

There were no significant differences between groups in terms of body weights or survival times ($p<0.05$). A dose-related increase in primary lung carcinomas was seen. Lung carcinoma incidences were 0/38, 6/39, 20/38 and 25/35 for the 0, 13.4, 25.7 and 50.8 $\mu g/m^3$ cadmium chloride groups, respectively.

4.3. OTHER RELEVANT DATA

The results of mutagenicity studies with cadmium are summarized in Tables 4-1 through 4-5. It is obvious that the results obtained in a variety of tests have been conflicting. It appears that cadmium is mutagenic in some test systems under some conditions; however, the relationship

TABLE 4-1

Mutagenicity of Cadmium: Evaluations Using Prokaryotes*

Test Organism	Cadmium Compound	Activation	Results
Salmonella typhimurium	aqueous cadmium chloride	phenobarbitol-induced rat liver	negative
Salmonella typhimurium	cadmium red in DMSO	Aroclor-induced mouse liver	negative
Salmonella typhimurium	cadmium chloride	uninduced mouse liver	negative
Salmonella typhimurium	cadmium diethyl-thiocarbamate in DMSO	Aroclor-induced rat liver	one dose positive, no dose response
Bacillus subtilis	aqueous cadmium chloride	none	weakly positive
Bacillus subtilis	aqueous cadmium nitrate	none	negative
Bacillus subtilis	cadmium chloride, nitrate and sulfite	none	weakly positive

*Source: U.S. EPA, 1984

TABLE 4-2

Mutagenicity of Cadmium: Evaluations Using Eukaryotic Cells*

Test System	Cadmium Compound	Results
Saccharomyces cerevisiae	cadmium chloride	positive
Saccharomyces cerevisiae	cadmium chloride	negative
Mouse lymphoma	cadmium chloride	weakly positive
Mouse lymphoma	cadmium sulfate	positive
Chinese hamster, lung	cadmium acetate, cadmium chloride	positive
Chinese hamster, ovary	cadmium chloride	weakly positive
Chinese hamster, V79	cadmium chloride	positive

*Source: U.S. EPA, 1984

TABLE 4-3

Mutagenicity of Cadmium: Evaluations Using Insects*

Organism	Test System	Compound	Results
Drosophila melanogaster	sex-linked recessive lethal	cadmium chloride	negative
Drosophila melanogaster	larval development sex-linked recessive lethal, sex chromosome loss	cadmium chloride	negative
Drosophila melanogaster	dominant lethal	cadmium chloride	positive
Drosophila melanogaster	sex-linked recessive lethal	cadmium stearate	negative
Drosophila melanogaster	sex chromosome loss	cadmium chloride	negative
Drosophila melanogaster	sex-linked recessive lethal	cadmium chloride	negative
Poekilocerus pictus	testicular meiotic chromosomes	cadmium chloride	positive

*Source: U.S. EPA, 1984

TABLE 4-4

Mutagenicity of Cadmium: *In vitro* Chromosome Aberrations*

Test Cells	Cadmium Compound	Results
Human lymphocytes	cadmium sulfide	positive
Human lymphocytes	cadmium chloride	negative
Human lymphocytes	cadmium chloride	negative
WI38 and MCR5	cadmium chloride	negative
Human lymphocytes (G_0 stage)	cadmium acetate	weakly positive
Chinese hamster HY cells	cadmium sulfate	positive
Chinese hamster CHO cells	cadmium chloride	positive with newborn calf or human serum, negative with fetal calf serum
Mouse mammary carcinoma, FM3A	cadmium chloride	negative

*Source: U.S. EPA, 1984

TABLE 4-5

Mutagenicity of Cadmium: *In vivo* Mammalian Systems*

Organism	Endpoint	Test Compound	Results
Mouse	bone marrow cells	cadmium chloride	negative
Mouse	bone marrow micronuclei	cadmium chloride	negative
Mouse	dominant lethals	cadmium chloride	negative
Mouse	dominant lethal	cadmium chloride	negative
Mouse	post-implantation loss	cadmium chloride	negative
Mouse	heritable translocation	cadmium chloride	negative
Mouse	spermatocytes	cadmium chloride	negative
Mouse	oocytes	cadmium chloride	positive
Mouse	blastocysts	cadmium chloride	positive for aneuploidy
Syrian hamster	oocytes	cadmium chloride	positive

*Source: U.S. EPA, 1984

between mutagenicity and carcinogenicity is not as well established for metals as for some other classes of carcinogens. McCann et al. (1975) reported that 75% of the metal carcinogens tested in the standard Ames test produced negative results.

For a thorough review of the available literature concerning cadmium mutagenicity, the reader is referred to U.S. EPA (1984). The preceding tables, adapted from the CAG document, are meant only to illustrate the scope of the testing effort and a general idea of the results. As can be readily seen, cadmium compounds have been extensively evaluated and most types of mutagenicity screening systems have produced mixed results. In addition to the material in the tables, evaluation of lymphocytes from occupationally exposed workers has produced equivocal results and tests for chromosomal aberrations in plants have in general been positive (U.S. EPA, 1984).

4.4. WEIGHT OF EVIDENCE

IARC (1982) has classified cadmium and certain cadmium compounds as group 2B chemicals. They considered the evidence for carcinogenicity to humans to be "limited," since it is "still far from clear which were the target organs for the putative carcinogenic action of cadmium in humans." Evidence for carcinogenicity in animals was considered "sufficient" based upon subcutaneous and intramuscular injection studies, which were not reviewed for this document (U.S. EPA, 1980b). Evidence for activity in short-term tests was considered "inadequate" because of the conflicting results reported by various authors (see Section 4.3.). Applying the classification criteria proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984) for evaluating the overall weight of evidence of carcinogenicity to humans, cadmium and compounds are most appropriately classified a Group B1, a probable human carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

The current regulatory standards and criteria are presented in Table 5-1. Values for water concentrations range from 0.7-10 µg/ℓ; recommended occupational air concentrations range from 0.12-100 µg/m³.

TABLE 5-1

Regulatory Standards, Limits or Criteria for Human Health Protection[a]

Media			
Air (inhalation)	Water (ingestion)	Food (ingestion)	Reference
100 µg/m³[b]	NR	NR	NIOSH, 1974
40 µg/m³	NR	NR	NIOSH, 1976
NR	10 µg/ℓ	NR	U.S. EPA, 1975
NR	NR	0.5 µg/mℓ[c]	FDA, 1974
NR	10 µg/ℓ	NR	WHO, 1971
50 µg/m³	NR	NR	ACGIH, 1977
0.12 µg/m³	WH1-1.9 µg/ℓ[d] WH2-0.7 µg/ℓ[d]	NR NR	MEG/EPC, 1977
NR	10 µg/ℓ	NR	NAS, 1972
NR	1 µg/ℓ[e]	NR	Krasovskii et al., 1976
NR	10 µg/ℓ	NR	Canada, 1969
NR	5 µg/ℓ (streams)	NR	Lykins and Smith, 1976[f]
NR	10 µg/ℓ	NR	U.S. EPA, 1980b
TLV = 0.05 mg/m³	NR	NR	ACGIH, 1980

TABLE 5-1 (cont.)

Media			
Air (inhalation)	Water (ingestion)	Food (ingestion)	Reference
STEL = 0.2 mg/m³	NR	NR	ACGIH, 1980
Ceiling Limit[g] = 0.05 mg/m³	NR	NR	ACGIH, 1983
40 µg/m³	NR	NR	NIOSH, 1976

[a]Adapted from U.S. EPA, 1980b

[b]For cadmium fume. Limit for cadmium dust is 200 µg/m³.

[c]Based on ceramic pottery and enamelware leaching solution test.

[d]EPC (estimated permissible concentration) WH1 is derived from the assumption that the maximum daily safe dosage results from 24-hour exposure to air containing the estimated permissible concentration in air, assuming 100% absorption, and that the same dose is therefore permissible in the volume of water consumed per day; WH2 is the estimated permissible concentration of the substance in water based on considerations of the safe maximum body concentration and the biological half-life of the substance.

[e]USSR (suggested)

[f]Ohio

[g]Cadmium oxide fumes

NR = Not reported

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. Since at present there is chronic baseline exposure of the human population (primarily through food) and since the critical effects of cadmium are dependent upon reaching a critical body burden, development of a separate subchronic estimate is not recommended.

6.1.2. Inhalation. Cadmium is a metal that is a known carcinogen through the inhalation route and for which data are sufficient for computing a q_1^*. It is, therefore, inappropriate to calculate an oral or inhalation AIS for cadmium.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. U.S. EPA (1980b) has proposed a drinking water criterion level of 10 µg/ℓ cadmium. Assuming an adult water consumption of 2 ℓ/day this would contribute 20 µg/day to the daily exposure in addition to food (major source) and ambient air. Therefore, it is suggested that 20 µg/ℓ be applied as the maximum additional increment from drinking water sources. U.S. EPA is in the process of developing a Recommended Maximum Contaminant Level (RMCL) for cadmium. When this value to published it should supercede the value proposed here.

6.2.2. Inhalation. Cadmium is a metal that is a known carcinogen through the inhalation route and for which data are sufficient for computing a q_1^*. It is, therefore, inappropriate to calculate an oral or inhalation AIC for cadmium.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Cadmium has not been shown to be carcinogenic in laboratory animals by oral administration. There are no human data (U.S. EPA, 1984).

Using the dose data for rats from Schroeder et al. (1965) and assuming a 10% upper limit of detection of tumors, CAG (U.S. EPA, 1984) has estimated an upper limit for the carcinogenic potency of ingested cadmium which is 2 orders of magnitude less than for inhalation. It is possible that as a result of extremely poor absorption from the GI tract, cadmium is not carcinogenic when ingested; however, the negative data available at this time can only be used to set an upper limit on potency. For these reasons, quantitative risk assessment for oral exposure to cadmium is impractical at the present time as a result of inadequate data.

6.3.2. Inhalation. The data of Takenaka et al. (1983) for induction of lung carcinoma in rats could be used for quantitative risk assessment. However, the CAG (U.S. EPA, 1984) felt that an extrapolation based on the human data for respiratory cancer (Thun et al., 1984) provided a more realistic assessment. Since this opinion was based on an in-depth, critical review of the literature which far exceeded the scope of the current document, this approach will be adopted here.

Using these data, CAG (U.S. EPA, 1984) has estimated that the most plausible estimate for the upper-bound unit risk for continuous inhalation exposure to 1 $\mu g/m^3$ cadmium to be 2.228×10^{-3}. This corresponds to a unit risk in units of $(mg/kg/day)^{-1}$ of 7.8.

7. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1977. TLVs. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1977. Cincinnati, OH. (Cited in U.S. EPA, 1980b)

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values for Substances in Workroom Air, 4th ed. with supplements through 1981. Cincinnati, OH. p. 59-61. (Cited in U.S. EPA, 1983a)

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. Threshold Limit Values for Chemical Substances in the Work Environment Adopted by ACGIH for 1984, 1985.

Ando, M., et al. 1977. Studies on excretion and uptake of calcium by rats after continuous oral administration of cadmium. Toxicol. Appl. Pharmacol. 39: 321. (Cited in U.S. EPA, 1980b)

Baader, E.W. 1952. Chronic cadmium poisoning. Ind. Med. Surg. 21: 427. (Cited in U.S. EPA, 1980b)

Banis, R.J., et al. 1969. Dietary cadmium, iron, and zinc interactions in the growing rat. Proc. Soc. Exp. Biol. Med. 130: 802. (Cited in U.S. EPA, 1980b)

Bremner, I. 1974. Heavy metal toxicities. Q. Rev. Biophys. 7: 75-124. (Cited in U.S. EPA, 1980b)

Bunn, C.R. and G. Matrone. 1966. In vivo interactions of cadmium, copper, zinc, and iron in the mouse and rat. J. Nutr. 90: 395. (Cited in U.S. EPA, 1980b)

Buxton, R.St.J. 1956. Respiratory function in cadmium alloy casters. Br. J. Ind. Med. 13: 36. (Cited in U.S. EPA, 1980b)

Callahan, M.A., M.W. Slimak, N.W. Gabel, et al. 1979. Water-Related Environmental Fate of 129 Priority Pollutants, Vol. I. Office of Water Planning and Standards, Office of Water and Waste Management, U.S. EPA, Washington, DC. EPA 440/4.790229a.

Canada. 1969. Canadian Drinking Water Standards and Objectives for 1968. Published by authority of Minister of National Health and Welfare. (Cited in U.S. EPA, 1980b)

Decker, L.E., R.U. Byerrum, C.F. Decker, C.A. Hoppert and R.F. Langham. 1958. Chronic toxicity studies. I. Cadmium administered in drinking water to rats. Arch. Ind. Health. 18: 228-231. (Cited in U.S. EPA, 1982)

Dixon, R.L., et al. 1976. Methods to assess reproductive effects of environmental chemicals: Studies of cadmium and boron administered orally. Environ. Health Perspect. 13: 59. (Cited in U.S. EPA, 1980b)

Elinder, C.G., et al. 1976. Cadmium in kidney cortex, liver, and pancreas from Swedish autopsies. Arch. Environ. Health. 30: 292. (Cited in U.S. EPA, 1980b)

FDA (Food and Drug Administration). 1974. Total diet studies (7320.08). Compliance Program Evaluation, Bur. Foods. (Cited in U.S. EPA, 1980b)

Federal Register. 1984. Environmental Protection Agency. Proposed guidelines for carcinogenic risk assessment. Federal Register 49: 46294-46299.

Ferm, V.H. and S.J. Carpenter. 1967. Teratogenic effect of cadmium and its inhibition by zinc. Nature. 216: 1123. (Cited in U.S. EPA, 1980b)

Fishbein, L. 1981. Sources, transport and alterations of metal compounds: An overview. I. Arsenic, beryllium, cadmium, chromium and nickel. Environ. Health Perspect. 40: 43-64.

Fitzhugh, O.G. and F.H. Meiller. 1941. The chronic toxicity of cadmium. J. Pharm. Exp. Ther. 72: 15. (Cited in U.S. EPA, 1983a)

Fox, M.R.S. and B.E. Fry. 1970. Cadmium toxicity decreased by dietary ascorbic acid supplements. Science. 169: 989.

Friberg, L. 1948a. Proteinuria and kidney injury among workers exposed to cadmium and nickel dust. J. Ind. Hyg. 30: 32-36. (Cited in U.S. EPA, 1980b)

Friberg, L. 1948b. Proteinuria and kidney injury among workers exposed to cadmium and nickel dust in a storage battery plant. Proc. Int. Congr. Ind. Med. 9: 641. (Cited in U.S. EPA, 1980b)

Friberg, L. 1950. Health hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning -- A clinical and experimental study. Acta Med. Scand. 138 Supplement CCXL. (Cited in U.S. EPA, 1980b)

Friberg, L., M. Piscator, G.F. Nordberg and T. Kjellstrom. 1974. Cadmium in the Environment, 2nd ed. CRC Press, Cleveland, OH. (Cited in U.S. EPA, 1980b)

Gunn, S.A., T.C. Gould and W.A.D. Anderson. 1963a. Cadmium-induced interstitial cell tumors in rats and mice and their prevention by zinc. J. Natl. Cancer Inst. 31: 745-759. (Cited in U.S. EPA, 1980b)

Gunn, S.A., T.C. Gould and W.A.D. Anderson. 1963b. The selective injurious response of testicular and epididymal blood vessels to cadmium and its prevention by zinc. Am. J. Path. 42: 685-693. (Cited in U.S. EPA, 1980b)

Gunn, S.A., et al. 1964. Effect of zinc on cancerogenesis by cadmium. Proc. Soc. Exp. Biol. Med. 115: 653. (Cited in U.S. EPA, 1980b)

Hill, C.H., G. Matrone, W.L. Payne and C.W. Barber. 1963. *In vivo* interactions of cadmium with copper, zinc, and iron. J. Nutr. 80: 227-235. (Cited in U.S. EPA, 1980b)

Holden, H. 1965. Cadmium fume. Ann. Occup. Hyg. 8: 51-54. (Cited in U.S. EPA, 1980b)

Hollander, M.L. and S.C. Carapella, Jr. 1978. Cadmium and cadmium alloys. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 4, M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., NY. p. 387-396.

IARC (International Agency for Research on Cancer). 1976. Cadmium and compounds. In: Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals, and General Considerations on Volatile Anaesthetics. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. WHO, IARC, Lyon, France. Vol. 11, p. 39-76. (Cited in U.S. EPA, 1983a)

IARC (International Agency for Research on Cancer). 1982. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. WHO, IARC, Lyon, France. IARC Monographs Supplement 4.

Kajikawa, K., I. Nakanishi and K. Kuroda. 1981. Morphological changes of the kidney and bone of rats in chronic cadmium poisoning. Exp. Molec. Pathol. 34: 9-24. (Cited in U.S. EPA, 1983a)

Kanisawa, M. and H.A. Schroeder. 1969. Life term studies on the effect of trace elements on spontaneous tumors in mice and rats. Cancer Res. 29: 892-895. (Cited in U.S. EPA, 1982)

Kazantzis, G., et al. 1963. Renal tubular malfunction and pulmonary emphysema in cadmium pigment workers. Q. J. Med. New Series. 32: 165. (Cited in U.S. EPA, 1980b)

Kobayashi, J. 1970. Relation between the "itai-itai" disease and the pollution of river water by cadmium from a mine. Proc. Int. Water Pollut. Res. Conf. I-25/1-7. (Cited in U.S. EPA, 1980b)

Koller, L.D., J.H. Exon and J.G. Roan. 1975. Antibody suppression by cadmium. Arch. Environ. Health. 30: 598-601.

Krasovskii, G.N., et al. 1976. Toxic and gonadotropic effects of cadmium and boron relative to standards for these substances in drinking water. Environ. Health Perspect. 13: 69. (Cited in U.S. EPA, 1980b)

Lane, R.E. and A.C.P. Campbell. 1954. Fatal emphysema in two men making a copper cadmium alloy. Br. J. Ind. Med. 11: 118. (Cited in U.S. EPA, 1980b)

Lauwerys, R., J.P. Buchet, H.A. Roels, J. Brouwers and D. Stanescu. 1974. Epidemiological survey of workers exposed to cadmium -- Effect on lung, kidney, and several biologic indices. Arch. Environ. Health. 28: 145-148. (Cited in U.S. EPA, 1980b, 1983a)

Levy, L.S. and J. Clark. 1975. Further studies on the effect of cadmium on the prostate gland. I. Absence of prostatic changes in rats given oral cadmium sulphate for two years. Ann. Occup. Hyg. 17: 205-211. (Cited in IARC, 1976; U.S. EPA, 1982)

Levy, L.S., J. Clark and F.J.C. Roe. 1975. Further studies on the effect of cadmium on the prostate gland. II. Absence of prostatic changes in mice given oral cadmium sulphate for eighteen months. Ann. Occup. Hyg. 17: 213-220. (Cited in IARC, 1976; U.S. EPA, 1982)

Lewis, G.P., H. Lyle and S. Miller. 1969. Association between elevated hepatic water-soluble protein-bound cadmium levels and chronic bronchitis and/or emphysema. Lancet. 2: 1330-1333. (Cited in U.S. EPA, 1980b)

Loser, E. 1980. A 2-year oral carcinogenicity study with cadmium in rats. Cancer Lett. 9(3): 191-198. (Cited in U.S. EPA, 1982)

Lykins, B.W., Jr. and J.M. Smith. 1976. Interim Report on the Impact of Public Law 92-500 on Municipal Pollution Control Technology. EPA 600/2-76-018. (Cited in U.S. EPA, 1980b)

McCann, J., E. Choi, E. Yamasaki and B.N. Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. 72: 5135-5139. (Cited in U.S. EPA, 1980b)

McLellan, J.S., et al. 1978. Measurement of dietary cadmium in humans. J. Toxicol. Environ. Health. 4: 131. (Cited in U.S. EPA, 1980b)

MEG/EPC (Multimedia Environmental Goals for Environmental Assessment). 1977. IERL, U.S. EPA, Research Triangle Park, NC. EPA 600/7-77-136. (Cited in U.S. EPA, 1980b)

Muramatsu, S. 1974. Research about cadmium-pollution in the Kakehashi River basin. Jap. J. Pub. Health. 21: 299. (Cited in U.S. EPA, 1980b)

NAS (National Academy of Sciences). 1972. Water quality criteria. A Report of the Committee on Water Quality Criteria. Cadmium. (Cited in U.S. EPA, 1980b)

NIOSH (National Institute for Occupational Safety and Health). 1974. Registry of Toxic Effects of Chemical Substances. U.S. DHEW, PHS, CDC. Rockville, MD.

NIOSH (National Institute for Occupational Safety and Health). 1976. Criteria for a Recommended Standard...Occupational Exposure to Cadmium. U.S. DHEW, PHS, CDC, Rockville, MD. Publ. No. 76-192. (Cited in U.S. EPA, 1980b, 1983a)

Nogawa, K., et al. 1978. Statistical observations of the dose-response relationships of cadmium based on epidemiological studies in the Kakehashi River basin. Environ. Res. 15: 185. (Cited in U.S. EPA, 1980b)

Page, G.W. 1981. Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ. Sci. Technol. 15: 1475-1481.

Parizek, J. 1957. The destructive effect of cadmium ion on testicular tissue and its prevention by zinc. J. Endocrin. 15: 56. (Cited in U.S. EPA, 1980b)

Parizek, J., et al. 1969. Metabolic interrelationships of trace elements. Effects of zinc salts on the survival of rats intoxicated with cadmium. Physiologia Bohemoslov. 18: 89. (Cited in U.S. EPA, 1980b)

Paterson, J.C. 1947. Studies on the toxicity of inhaled cadmium. III. The pathology of cadmium smoke poisoning in man and in experimental animals. J. Ind. Hyg. Toxicol. 29: 294. (Cited in U.S. EPA, 1980b, 1982)

Potts, C.L. 1965. Cadmium proteinuria -- The health of battery workers exposed to cadmium oxide dust. Ann. Occup. Hyg. 8: 55-61. (Cited in U.S. EPA, 1980b)

Rahola, T., et al. 1973. Retention and elimination of ^{155m}Cd in man. In: Health Physics Problems of Internal Contamination. Akademiai Kiado, Budapest. (Cited in U.S. EPA, 1980b)

Sato, K. 1977. Peripheral nerve lesions and carcinogenesis after long-term administration of cadmium in the rat. Kumamoto Med. J. 51(4): 242-264. (Cited in U.S. EPA, 1982)

Schroeder, H.A. and M. Mitchener. 1971. Toxic effects of trace elements on the reproduction of mice and rats. Arch. Environ. Health. 23: 102-106. (Cited in U.S. EPA, 1980b, 1983a)

Schroeder, H.A., W.H. Vinton and J.J. Balassa. 1963. Effects of chromium, cadmium, and lead on the growth and survival of rats. J. Nutr. 80: 48-54. (Cited in U.S. EPA, 1983a)

Schroeder, H.A., J.J. Balassa and W.H. Vinton, Jr. 1964. Chromium, lead, cadmium, nickel and titanium in mice: Effect on mortality, tumors and tissue levels. J. Nutr. 83: 239-250. (Cited in U.S. EPA, 1982, 1983a)

Schroeder, H.A., J.J. Balassa and W.H. Vinton, Jr. 1965. Chromium, cadmium and lead in rats: Effects on life span, tumors and tissue levels. J. Nutr. 86: 51-66. (Cited in U.S. EPA, 1982, 1983a)

Smith, J.P., J.C. Smith and A.J. McCall. 1960. Chronic poisoning from cadmium fume. J. Path. Bact. 80: 287-296. (Cited in U.S. EPA, 1980b)

Smith, T.J., et al. 1976. Pulmonary effects of chronic exposure to airborne cadmium. Am. Rev. Resp. Dis. 114: 161. (Cited in U.S. EPA, 1980b)

Snider, G.G., et al. 1973. Centrilobular emphysema experimentally induced by cadmium chloride aerosol. Am. Rev. Resp. Dis. 108: 40. (Cited in U.S. EPA, 1980b)

Starcher, B.C. 1969. Studies on the mechanism of copper absorption in the chick. J. Nutr. 97: 321-326. (Cited in U.S. EPA, 1980b)

Suzuki, S., et al. 1969. Dietary factors influencing upon retention rate of orally administered $^{155m}CdCl_2$ in mice with special reference to calcium and protein concentrations in diet. Ind. Health. 7: 155. (Cited in U.S. EPA, 1980b)

Takenaka, S., H. Oldiges, H. Konig, D. Hochrainer and G. Oberdoerster. 1983. Carcinogenicity of cadmium aerosols in Wistar rats. J. Natl. Cancer Inst. 70: 367-373.

Thun, M.J., T.M. Schnorr, A.B. Smith and W.E. Halperin. 1984. Mortality among a cohort of U.S. cadmium production workers: An update. NIOSH, Washington, DC. (Unpublished) (Cited in U.S. EPA, 1984)

Tshuchiya, K. 1967. Proteinuria of workers exposed to cadmium fume -- The relationship to concentration in the working environment. Arch. Environ. Health. 14: 875-880. (Cited in NIOSH, 1976; U.S. EPA, 1983a)

U.S. EPA. 1975. Scientific and technical assessment report on cadmium. National Environmental Research Center, Research Triangle Park, NC. EPA 600/6-75-003. (Cited in U.S. EPA, 1980b)

U.S. EPA. 1980a. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Quality Criteria. Federal Register. 45:79347-79357.

U.S. EPA. 1980b. Ambient Water Quality Criteria for Cadmium. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-025. NTIS PB 81-117368.

U.S. EPA. 1982. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of Cadmium and Compounds. Prepared by Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983a. Reportable Quantity for Cadmium (and compounds). Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983b. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Updated mutagenicity and carcinogenicity assessment of cadmium. Carcinogen Assessment Group, OHEA. EPA 600/8-83-025B. NTIS PB 85-116150.

Washko, P.W. and R.J. Cousins. 1976. Metabolism of ^{109}Cd in rats fed normal and low-calcium diets. J. Toxicol. Environ. Health. 1: 1055. (Cited in U.S. EPA, 1980b)

Worker, N.A. and B.B. Migicovsky. 1961. Effect of vitamin D on the utilization of zinc, cadmium and mercury in the chick. J. Nutr. 75: 222. (Cited in U.S. EPA, 1980b)

WHO (World Health Organization.) 1971. International Standards for Drinking Water, 3rd ed. WHO, Geneva. (Cited in U.S. EPA, 1980b)

WHO (World Health Organization) Task Group. 1977. Environmental health aspects of cadmium. WHO, Geneva. (Cited in U.S. EPA, 1980b)

Yuhas, E.M., T.S. Miya and R.C. Schnell. 1979. Dose-related alterations in growth and mineral disposition by chronic oral cadmium administration in the male rat. Toxicology. 12: 19-29. (Cited in U.S. EPA, 1983a)

APPENDIX

Summary Table for Cadmium
Carcinogenic Effects

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	Unit Risk or q_1*	Reference
Inhalation				7.8 $(mg/kg/day)^{-1}$	Thun et al., 1984; U.S. EPA, 1984
Oral				ND*	

*Evidence is inadequate to consider cadmium a carcinogen through the oral route. The additional exposure increment through drinking water should be restricted to correspond to 10 µg/ℓ (U.S. EPA, 1980b).

ND = Not derived